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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/942,098	08/28/2001	Lance E. Steward	17451 (BOT)	6185

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/942,098	STEWARD ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2006*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8,45-53,55,57-64,96-122 and 126-178* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8,45-53,55,57-64,96-122,126-144,149-154 and 160-164* is/are rejected.

7)☒ Claim(s) *145-148,155-159 and 165-178* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 17, 2006 has been entered.

2. Applicants' amendment filed January 17, 2006 is acknowledged and has been entered. Claims 1-3, 9-44, 54, 56, 65-95 and 123-125 have been canceled. Claims 102, 168 and 169 have been amended. New claims 176-178 have been added. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Misnumbered claim 177 (the second recitation of 177) has been renumbered 178. Claims 4-8, 45-53, 55, 57-64, 96-122 and 126-178 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.

3. Applicant's species election of SEQ ID NO: 29, 90-93, amino acids 191-202 of SEQ ID NO: 2 and amino acids 187-203 of SEQ ID NO: 2 in the reply filed on

January 17, 2996 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). SEQ ID NO: 1, 2, 29, 30, 90-93, amino acids 191-202 of SEQ ID NO: 2 and amino acids 187-203 of SEQ ID NO: 2 are being examined in the pending application.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 4-8, 45-53, 55, 57-64, 96-101, 142-144, 149-154, 160-164 and 169-175 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With regard to claims 4-8, 45-53, 55, 57-64, 96-101 and 149-154, there is no support in the specification for the recitation of "at least 14 amino acids separate said donor fluorophore from said acceptor".

With regard to claims 169-175, there is no support for the recitation of "separated by at most fifty residues" (claim 169), "separated by at least 50 residues" (claim 170), "separated by at least 75 residues" (claim 171), "separated by at least 100 residues" (claim 172), "separated by at least 125 residues" (claim 173), "separated by at least 150 residues" (claim 174) and "separated by at least 200 residues" (claim 175). Paragraph [0041] of the specification teaches:

> "In other embodiments, the donor fluorophore and the acceptor are separated by at most six residues, at most eight residues, at most ten residues, at most twelve residues, at most fifteen residues, at most twenty residues, at most twenty-five residues, at most thirty residues, at most thirty-five residues or at most forty residues."

With regard to claims 142-144, there is no support found in the specification for the recitation of "a peptide having at most 500 residues" (claim 142), "a peptide having at most 600 residues" (claim 143) and " a peptide having at most 700 residues" (claim 144). Paragraph [0041] of the specification teaches:

> "In particular embodiments, a clostridial toxin substrate of the invention is has at most 20 residues, at most 40 residues, at most 50 residues, at most 100 residues, at most 150 residues, at most 200 residues, at most 250 residues, at most 300 residues, at most 350 residues or at most 400 residues."

With regard to claims 160-164, there is no support found in the specification for the recitation of "a peptide or peptidomimetic having at least 300 residues" (claim 160), "a peptide or peptidomimetic having at least 400 residues" (claim 161), "a peptide or peptidomimetic having at least 500 residues" (claim 162), "a peptide or peptidomimetic having at least 600 residues" (claim 163), "a peptide or peptidomimetic having at least 700 residues" (claim 164). Paragraph [0041] of the specification teaches:

> "In particular embodiments, a clostridial toxin substrate of the invention is has at most 20 residues, at most 40 residues, at most 50 residues, at most 100 residues, at most 150 residues, at most 200 residues, at most 250 residues, at most 300 residues, at most 350 residues or at most 400 residues.

With regard to claims 96-101, the claims recite that the substrate has a length of 19, 20, 21, 22, 69 or 72 amino acids, see claims 96-101 respectively.

However, the specification at paragraph [0080] teaches the use of a BoNT/A recognition sequence with various lengths for human SNAP-25, not for substrates.

> "[0080] A variety of BoNT/A recognition sequences are well known in the art. A BoNT/A recognition sequence can have, for example, residues 134 to 206 or residues 137 to 206 of human SNAP-25 (Ekong et al., supra, 1997; U.S. Pat. No. 5,962,637). A BoNT/A recognition sequence also can include, without limitation, the sequence Thr-Arg-Ile-Asp-Glu-Ala-Asn-Gln-Arg-Ala-- Thr-Lys-Met (SEQ ID NO: 27), or a peptidomimetic thereof, which corresponds to residues 190 to 202 of human SNAP-25; Ser-Asn-Lys-Thr-Arg-Ile-Asp-Glu-Ala-Asn-Gln-Arg-Ala-Thr-Lys (SEQ ID NO: 28), or a peptidomimetic thereof, which corresponds to residues 187 to 201 of human SNAP-25; Ser-Asn-Lys-Thr-Arg-Ile-Asp-Glu-Ala-Asn-Gln-Arg-Ala- -Thr-Lys-Met (SEQ ID NO: 29), or a peptidomimetic thereof, which corresponds to residues 187 to 202 of human SNAP-25; Ser-Asn-Lys-Thr-Arg-Ile-Asp-Glu-Ala-Asn-Gln-Arg-Ala-Thr-Lys-Met-Leu (SEQ ID NO: 30), or a peptidomimetic thereof, which corresponds to residues 187 to 203 of human SNAP-25; Asp-Ser-Asn-Lys-Thr-Arg-Ile-Asp-Glu-Ala-Asn-- Gln-Arg-Ala-Thr-Lys-Met (SEQ ID NO: 31), or a peptidomimetic thereof, which corresponds to residues 186 to 202 of human SNAP-25; or Asp-Ser-Asn-Lys-Thr-Arg-Ile-Asp-Glu-Ala-Asn-Gln-Arg-Ala-Thr-Lys-Met-Leu (SEQ ID NO: 32), or a peptidomimetic thereof, which corresponds to residues 186 to 203 of human SNAP-25. See, for example, Schmidt and Bostian, J. Protein Chem. 14:703-708 (1995); Schmidt and Bostian, supra, 1997; Schmidt et al., FEBS Letters 435:61-64 (1998); and Schmidt and Bostian, U.S. Pat. No. 5,965,699). If desired, a similar BoNT/A recognition sequence can be prepared from a corresponding (homologous) segment of another BoNT/A-sensitive SNAP-25 isoform or homolog such as, for example, murine, rat, goldfish or zebrafish SNAP-25 or can be any of the peptides disclosed herein or described in the art, for example, in U.S. Pat. No. 5,965,699."

6. Claims 102-112 and 118-122 are rejected under 35 U.S.C. 102(e) as being anticipated by Schmidt et al 6762280.

Schmidt et al discloses substrates for clostridial neurotoxins and that these substrates can be modified peptides or proteins that can serve as FRET substrates

(abstract; col. 4). Schmidt et al discloses that Botulinum serotype A cleaves the protein SNAP-25 and that because botulinum neurotoxins are proteases, practical assays for this activity could form the basis for detection, quantification and drug-screening systems (col. 1). Schmidt et al discloses substrate peptides suitable for use in fluorescence resonant energy transfer assays (FRET), also known as quenched-signal assays, for the protease activities of clostridial neurotoxins (col. 3). Schmidt et al discloses "FRET substrates for proteolytic activities of clostridial neurotoxins. Each contains a fluorescent group (fluorophore) on one side of the cleavage site, and a molecule that quenches that fluorescence on the other side of the cleavage site. Upon neurotoxin-catalyzed hydrolysis, the fluorophore and quencher diffuse away from each other, and the fluorescence signal increases in proportion to the extent of hydrolysis." (col. 5 ; see also col. 7). The amino acid sequences set forth in pending claims 102-104 are in Schmidt et al (see Schmidt et al SEQ ID NO: 11 and 12). The human SNAP-25 sequence is disclosed in Schmidt et al. The prior art anticipates the claimed invention. It is noted that none of these claims recite how many amino acids should separate the donor fluorophore from said acceptor.

7. Claims 102 and 113-117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al 6762280 taken with Holskin et al 1995 (Analytical Biochemistry, 226:148-155).

Schmidt et al teaches substrates for clostridial neurotoxins and that these substrates can be modified peptides or proteins that can serve as FRET substrates (abstract; col. 4). Schmidt et al teaches that Botulinum serotype A cleaves the protein SNAP-25 and that because botulinum neurotoxins are proteases, practical

assays for this activity could form the basis for detection, quantification and drug-screening systems (col. 1). Schmidt et al teaches substrate peptides suitable for use in fluorescence resonant energy transfer assays (FRET), also known as quenched-signal assays, for the protease activities of clostridial neurotoxins (col. 3). Schmidt et al teaches "FRET substrates for proteolytic activities of clostridial neurotoxins. Each contains a fluorescent group (fluorophore) on one side of the cleavage site, and a molecule that quenches that fluorescence on the other side of the cleavage site. Upon neurotoxin-catalyzed hydrolysis, the fluorophore and quencher diffuse away from each other, and the fluorescence signal increases in proportion to the extent of hydrolysis." (col. 5; see also col. 7). The amino acid sequences set forth in pending claims are in Schmidt et al (see Schmidt et al SEQ ID NO: 11 and 12; cols. 7-8). The human SNAP-25 sequence is taught in Schmidt et al. It is noted that none of these claims recite how many amino acids should separate the donor fluorophore from said acceptor. The prior art teaches the claimed invention except for the specific fluorophores of EDANS and DABCYL.

However, Holskin et al teaches substrates that comprise a donor fluorophore, acceptor fluorophore and a protease having a specific cleavage site (abstract). Holskin et al teaches the specific fluorophores of EDANS and DABCYL (abstract). Holskin et al teaches that donor and acceptor pair EDANS and DABCYL, respectively, have excellent spectral overlap properties resulting in efficient energy transfer and that strategies incorporating this donor/acceptor pair have been successfully applied to fluorescence-based assays for HIV protease, renin as well as others (p. 149, col. 1; p. 152). It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of Schmidt et al with Holskin et al to prepare a substrate complex as

taught in Schmidt et al and Holskin et al, a fluorescence-based assay, which has the donor and acceptor fluorophores and the substrate with the substrate being a clostridial toxin. Although Holskin et al does not specifically teach BoNT/A the prior art does teach this concept with several other proteins and substrates to assay for potency of therapeutic compositions and to monitor potential inhibitors. Therefore, the use of SNAP-25 and BoNT/A in a similar substrate complex would have been obvious to a person of ordinary skill in the art with the reasonable expectation of success since it had been proven successful in other substrate compositions; especially in view of the fact that Schmidt et al teaches the use of FRET assays to monitor for therapeutic compositions or potential inhibitors. The claimed invention is prima facie obvious in view of the prior art teachings as a whole, absent any unexpected evidence to the contrary.

8. Claims 126-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al (6762280), Holskin et al 1995 (Analytical Biochemistry, 226:148-155) taken with Mahajan et al (Chemistry and Biology, 1999, 6:401-409).

Schmidt et al teaches substrates for clostridial neurotoxins and that these substrates can be modified peptides or proteins that can serve as FRET substrates (abstract; col. 4). Schmidt et al teaches that Botulinum serotype A cleaves the protein SNAP-25 and that because botulinum neurotoxins are proteases, practical assays for this activity could form the basis for detection, quantification and drug-screening systems (col. 1). Schmidt et al teaches substrate peptides suitable for use in fluorescence resonant energy transfer assays (FRET), also known as quenched-signal assays, for the protease activities of clostridial neurotoxins (col. 3). Schmidt et al teaches "FRET substrates for proteolytic activities of clostridial

neurotoxins. Each contains a fluorescent group (fluorophore) on one side of the cleavage site, and a molecule that quenches that fluorescence on the other side of the cleavage site. Upon neurotoxin-catalyzed hydrolysis, the fluorophore and quencher diffuse away from each other, and the fluorescence signal increases in proportion to the extent of hydrolysis." (col. 5; see also col. 7). The amino acid sequences set forth in pending claims are in Schmidt et al (see Schmidt et al SEQ ID NO: 11 and 12; cols. 7-8). The human SNAP-25 sequence is taught in Schmidt et al. The claims also recite the defined sequence or a peptidomimetic thereof, which would be any variation of the BoNT/A taught or suggested in Schmidt et al. It is noted that none of these claims recite how many amino acids should separate the donor fluorophore from said acceptor. Holskin et al teaches substrates that comprise a donor fluorophore, acceptor fluorophore and a protease having a specific cleavage site (abstract). Holskin et al teaches the specific fluorophores of EDANS and DABCYL (abstract). Holskin et al teaches that donor and acceptor pair EDANS and DABCYL, respectively, have excellent spectral overlap properties resulting in efficient energy transfer and that strategies incorporating this donor/acceptor pair have been successfully applied to fluorescence-based assays for HIV protease, renin as well as others (p. 149, col. 1; p. 152).

Mahajan et al teaches, as stated in the specification (p. 86), donor fluorophore or acceptor can be a genetically encoded dye such as green fluorescence protein (GFP), blue fluorescence protein (BFP), cyan fluorescence protein (CFP), yellow fluorescence protein (YFP) or red fluorescence protein. Such genetically encoded donor fluorophores and acceptors are well known in the art as described in Mahajan et al. The prior art teaches that this type of technology

(labeling substrates, proteins or DNA with fluorescence for use in assays) with can be used in screening of reagents or for diagnostic purposes.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of Schmidt et al with Holskin et al to prepare a substrate complex as taught in Schmidt et al and Holskin et al, a fluorescence-based assay, which has the donor and acceptor fluorophores and the substrate with the substrate being a clostridial toxin. Although Holskin et al does not specifically teach BoNT/A the prior art does teach this concept with several other proteins and substrates to assay for potency of therapeutic compositions and to monitor potential inhibitors. Therefore, the use of SNAP-25 and BoNT/A in a similar substrate complex would have been obvious to a person of ordinary skill in the art with the reasonable expectation of success since it had been proven successful in other substrate compositions; especially in view of the fact that Schmidt et al teaches the use of FRET assays to monitor for therapeutic compositions or potential inhibitors. Mahajan et al teaches that the donor or acceptor fluorophores can be genetically encoded, and that this technique can be used to study enzyme activity or monitor for reagents in a high-throughput screening process. Therefore, modification of the donors or acceptors is within the skill of a person of ordinary skill in the art at the time the invention was made. With regard to the specifically claimed number of amino acids in the substrate, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the number of amino acids in the substrate in view of the prior art teaching that the composition of the substrate can vary and since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. *In re Boesch*, 617 F.2d 272, 205 USPQ 215

(CCPA 1980). The claimed invention is prima facie obvious in view of the prior art teachings as a whole, absent any unexpected evidence to the contrary.

9. Claims 145-148, 155-159, 165-178 are objected to because they depend from a rejected claim.

10. No claims are allowed.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
April 11, 2006